Assessment of five screening strategies for optimal detection of carriers of third-generation cephalosporin-resistant *Enterobacteriaceae* in intensive care units using daily sampling

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Abstract

There is no consensus on optimal screening procedures for multidrug-resistant *Enterobacteriaceae* (MDRE) in intensive care units (ICUs). Therefore, we assessed five strategies for the detection of extended-spectrum beta-lactamase (ESBL) and high-level expressed AmpC cephalosporinase (HL-CASE) producers. During a 3-month period, a rectal screening swab sample was collected daily from every ICU patient, from the first 24 h to the last day of ICU stay. Samples were plated on MDRE-selective media. Bacteria were identified using MALDI-TOF mass spectrometry and antibiograms were performed using disk diffusion. MDREs were isolated from 682/2348 (29.0%) screening samples collected from 93/269 (34.6%) patients. Incidences of patients with ESBL and HL-CASE producers were 17.8 and 19.3 per 100 admissions, respectively. In 48/93 patients, MDRE carriage was intermittent. Compared with systematic screening at admission, systematic screening at discharge did not significantly increase the rate of MDRE detection among the 93 patients (62% vs. 70%). In contrast, screening at admission and discharge, screening at admission and weekly thereafter, and screening at admission and weekly thereafter and at discharge significantly increased MDRE detection (77%, p 0.02; 76%, p 0.01; 86%, p <0.001, respectively). The difference in MDRE detection between these strategies relies essentially on the levels of detection of patients with HL-CASE producers. The most reasonable strategy would be to collect two samples, one at admission and one at discharge, which would detect 87.5% of the ESBL strains, 67.3% of the HL-CASE strains and 77.4% of all MDRE strains. This study should facilitate decision-making concerning the most suitable screening policy for MDRE detection in a given ICU setting.

Keywords: cephalosporinase, extended-spectrum beta-lactamase, intensive care units, multidrug-resistant *Enterobacteriaceae*, screening strategies
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Introduction

While third-generation cephalosporins (3GCs) are the antimicrobial agents used most commonly for infections due to *Enterobacteriaceae*, the level and spread of 3GC resistance has become a major public health concern [1–3]. Two dominant mechanisms contribute to 3GC resistance in *Enterobacteriaceae*, the generally plasmid-mediated acquisition of extended-spectrum β-lactamase (ESBL)-encoding genes [1] and the high-level expression of AmpC cephalosporinase (HL-CASE) following either *in vivo* selected derepression of low-level expressed chromosome-encoded AmpC (LL-CASE) or, less frequently, acquisition of a plasmid-borne AmpC gene [1,4,5].

Resistance to 3GCs is often associated with resistance to other antibiotic families resulting in multidrug-resistant *Enterobacteriaceae* (MDRE). Before the spread of CTX-M-producing *Escherichia coli*, cross-contamination was the usual pathway for acquisition of ESBL-producing *Enterobacteriaceae* (ESBL strains) and hardly ever the consequence of *in vivo* selected mutation [1,6]. In contrast, *in vivo* selection remains the most common mode of HL-CASE production [7,8]. In recent years, a steady increase in the prevalence of ESBL strains has been observed in hospitals, long-term care facilities and in the community [9–11] while the prevalence of HL-CASE-producing *Enterobacteriaceae* (HL-CASE-strains) increased mainly in hospitals [5,12,13].

In intensive care units (ICUs), high MDRE prevalence has become a cause of increased morbidity and mortality, and a major concern with respect to the most appropriate treatment for infected patients [2,14–17]. Given the poor development of new drugs active against MDRE, the fight against their cross-transmission is of major importance. A better knowledge of the pattern of MDRE carriage in patients admitted to ICUs would help in selecting the best screening strategy in order to detect asymptomatic carriers, implement prompt isolation precautions and, thereby, limit MDRE spread [18,19]. While there is no definitive consensus on the most effective screening strategy for the detection of asymptomatic MDRE carriers [20], systematic screening at patient admission has been recommended [18,19,21]. However, this strategy does not take into account MDRE acquisition during patient stay.

With the aim of defining the most appropriate screening strategy for detection of asymptomatic MDRE carriers in ICUs, we performed a prospective study using systematic daily sampling during the entire stay of ICU patients.

Methods

Settings and patients

All patients admitted to the medical and the surgical ICUs of an 830-bed acute-care teaching hospital between 3 April and 3 July 2011 were included in the study and surveyed until discharge. Patients already present in the ICUs on 3 April, patients who died during the first day of their stay and patients who refused to participate were not included. The study complied with confidentiality regulations and ethical standards, and, in agreement with French regulations, the institutional review board waived the need for informed consent (CCPPRB project number: ID-RCB 201-A00259-32, University Paris XI, February 2011).

Screening

Using the eSwab® system (Copan, Brescia, Italy), a rectal screening swab (RSS) was collected daily from each patient between the first 24 h (admission RSS) and the last day in the ICU (discharge RSS). For patients admitted late in the evening of day 1, if no RSS was collected, the RSS collected on the next morning (day 2) was considered the admission RSS. For patients who died, an RSS was not systematically collected on the last day, and the RSS of the day before was considered to be the discharge RSS. Rectal screening results were provided to physicians and nurses.

Microbiological tests

Each RSS was suspended in 1 mL of Liquid Amies (Copan), and 10 μL of the suspension were plated on two selective media (ChromID®, bioMérieux, Lyon, France, and Drigalski agar ceftazidime, Becton Dickinson, Franklin Lakes, NJ, USA) using an automated specimen-plating device (WASP®; Copan, Milan, Italy). Colonies were picked after 18 h of incubation at 37°C. Isolates were identified using matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry with a Microflex Bruker Daltonics/BioTyper™ version 2.0 system (Bruker Daltoniks, Bremen, Germany). Antimicrobial susceptibility indicative of ESBL and/or HL-CASE production was tested with the disk diffusion method on Mueller–Hinton agar (MH; Bio-Rad, Marnes-la-Coquette, France), according to European guidelines [22]. An isolate was categorized as an ESBL producer when a zone of synergy between a 3GC or aztreonam and clavulanic acid disk was observed and as an HL-CASE producer when it displayed (i) resistance to 3GCs, (ii) absence of synergy between any 3GC or aztreonam and clavulanic acid, and (iii) at least a 5-mm increase in the inhibition zone diameters around the 3GC disks, observed on MH with and without cloxacillin (250 μg/mL). To reveal ESBL potentially masked by HL-CASE production, synergy was tested on MH with and without cloxacillin (250 μg/mL). All isolates categorized as ESBL and/or HL-CASE producers were also categorized collectively as MDRE.

Imported and acquired resistant strains

When the first RSS with an MDRE strain was collected on day 1 and/or day 2 (≤48 h), the corresponding strain was categorized as imported; when it was collected on or after day 3 (>48 h), the corresponding strain was categorized as acquired (by cross-transmission or *in vivo* selection). In a given patient, ESBL strains and HL-CASE strains could be imported or acquired independently.

Cross-transmission

When two isolates belonging to the same species and with the same antimicrobial resistance pattern were isolated from two